#2

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patent Office
Canberra

I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002952144 for a patent by PERFUSION DIAGNOSTICS PTY LTD as filed on 17 October 2002.

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

WITNESS my hand this
Sixth day of November 2003

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES

AUSTRALIA

Patents Act 1990

Perfusion Diagnostics Pty Ltd

PROVISIONAL SPECIFICATION

Invention Title:

Method and apparatus for measuring tissue perfusion

The invention is described in the following statement:

Field of the Invention

This invention relates to monitoring and diagnostic apparatus and in particular to a method and apparatus for measuring tissue perfusion and analysing blood flow changes as they occur in tissue perfusion.

Background of the Invention

The blood circulation is divided into two principal divisions. Firstly, the macrocirculation comprises the heart pump and peripheral arteries and veins for distribution of blood to and from the body tissues. Secondly, the microcirculation is a network system of small blood vessels and capillaries. Tissue Perfusion is blood flow through the microcirculation and tissue perfusion determines the viability of body tissues. Changes in microcirculation occur very early in the train of events leading to evidence of circulatory disturbance.

Non-invasive cardiovascular monitoring systems currently in widespread clinical application measure macroscopic parameters such as blood pressure, pulse rate, the Electrocardiogram (ECG) and tissue oxygen saturation (TOS%) which does not react to early falls in capillary blood flow. While these parameters provide important feedback to the clinician, they cannot reflect the vital activity of the highly sensitive microcirculation.

Figure 1 illustrates the relationship between the skin microcirculation and deeper vasculature. The invention non-invasively measures the change in capillary blood flow, at the very interface between the arterial and venous compartments of vascular system in all living tissue.

The human body has a wide variety of cardiovascular, respiratory and basic metabolic reflex mechanisms which endeavour to maintain constancy of blood supply to the vital organs. Because of the expendability of skin perfusion relative to the vital central organs such as the heart and brain, in the presence of cardiovascular threat, skin microcirculation is able to provide a reserve blood supply through an early compensatory vascoconstrictive mechanism. Monitoring macroparameters alone has the following disadvantages:

- Macroparameters are insensitive to compensatory changes in microcirculation, which affect tissue perfusion, until there is failure of one or more of these compensatory mechanisms which endeavour to maintain blood supply to the vital organs. By contrast, by monitoring the skin microcirculation, the clinician is able to observe the start of this compensatory activity to maintain blood supply to the vital organs, and

so therefore gains much earlier warning of any impending threat to physiological status.

- The macroparameters do not provide information that is specific to an area of interest (such as the border of a skin lesion or wound). By contrast, assessing the microcirculatory flow of a particular tissue provides direct confirmation that the targeted tissue is receiving nutrients and able to remove waste products. Furthermore, the microcirculatory flow of a targeted area can be compared with other reference areas of tissue.

US Patent 3,796,214 to F.R.N. Stephens discloses a monitoring system, known as the Stephens Tissue Perfusion Monitor or "STPM", which assesses microcirculatory blood flow in the capillary beds and US Patent 4,442,845 also to F.R.N. Stephens discloses a means of analysing the resulting signal curves. The entire contents of both specifications are incorporated herein by reference.

The STPM's basic parameter, the Tissue Perfusion Index (TPI) is derived from the microcirculation. The invention as described herein uses a non-invasive probe which provides a pulsed source of light and a matched sensor which transduces the variations in reflected light from the capillary bed into an electrical signal (called the signal pulse curve). The TPI is the short term average running product of a value for the area under the pulse curve and an immediate value for pulse rate per minute. As a result, the TPI provides a continuous quantitative measure of proportional changes, as they occur in blood flow through an observed capillary bed of tissue microcirculation, relative to an initial reference level of tissue perfusion.

Ongoing experience with the STPM has shown it invaluable for warning the clinician of subclinical trends in skin tissue perfusion which could threaten patient wellbeing. For example, steadily declining microcirculation from blood loss during surgery causing fall in TPI and no change in TOS, if uncorrected, can precede clinical shock. Unexpected surgical death occurs because of inability to maintain tissue perfusion. In cardiac shock disturbance of skin capillary circulation is observed and continuous surveillance of skin tissue perfusion, with TPI, provides a vital means of identifying trends in response to treatment.

The pathophysiological state of tissue cannot be assessed from macroparameters such as tissue oxygen saturation, pulse rate or blood pressure. This can be readily demonstrated using staged occlusion of the

brachial artery with a sphygmomanometer cuff, where it has been reproducibly observed that up to approximately 90% of capillary bed can close down before significant change occurs in tissue oxygen saturation (refer example data in Figure 11). In clinical application, it can therefore be appreciated that the parameters of tissue oxygen saturation, blood pressure, pulse and ECG, though important, cannot measure the early vital capillary flow changes of tissue perfusion which signal imminent shock. This is ordinarily because of the physiologically necessary, large capillary reserve.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

Summary of the Invention

In a broad aspect the present invention is directed to a method and apparatus, using a pulsed light source, for measuring microcirculatory flow of a target tissue without the necessity for direct contact of a probe.

According to a first aspect of the present invention there is provided an apparatus for monitoring tissue perfusion including:-

a probe, arranged to generate a pulsed source of infrared light, or light of other spectral wavelength and a matched infrared sensor, or sensor of other suitably matched peak response wavelength, which transduces variations in the reflected light to an electric signal which undergoes signal processing; and.

a signal processor, which receives the electric signal and compares the signal at a first time when the pulsed light source is on with a second time when the pulsed light is off, the first and second times being almost concurrent, and processes the signal to reduce or ameliorate the effect of the ambient light in the signal.

By comparing the signal obtained at these two points in time significant gains in signal to noise ratio can be obtained. Typically the processor digitally samples the signal and analyses it to calculate the Tissue Perfusion Index, as well as other measurements relating to the waveform.

The key advantage of the invention, described in this application, is that by using a pulsed light source and compensating for the background signal or

noise due to ambient light; measurement of microcirculatory flow can now be obtained without contact between the probe and the target tissue. This reduces the risk of contact artifact at the areas of microcirculation being analysed. Furthermore, because the probe need no longer contact the target tissue, the use of the apparatus is extended (for example to, chronic ulcers on the extremities, the surface of the retina, the vascular pulp within a tooth or the surface of internal organs, accessed by fiberoptic or endoscopic means). Finally it can now provide more exact and simpler targeting of accessible tissue for analysis of tissue perfusion (for example, angiogenesis at the border of skin grafts, burns or comparison of microcirculatory activity in or around various skin lesions).

Typically the apparatus will further include a display and/or warning system which at the user's discretion, displays either individual waveforms or selected combinations of waveforms, or a continuous single waveform with a running trace of the TPI trend. The system may be arranged so that selected characteristics of the waveform shape and/or changes in the TPI can activate an audible alarm when the measurement moves above or below pre-defined limits.

The light may or may not be monochromatic.

In a related aspect the present invention provides a method for measuring microcirculatory blood flow in a body comprising the steps of:

- using an emitter of pulsed light to irradiate an area of the body for measurement of microcirculatory changes;
- receiving light reflected from the area at a distance from the area being irradiated by the incident light; and
- determining from the reflected light a measure of the changes that correspond with the pulsatile filling and partial emptying of the microcirculation.

The method will further include the step of calculating the Tissue Perfusion Index and displaying key signal characteristics of said index.

Brief Description of the Drawings

Specific examples of the present invention will now be described, by way of example only, and with reference to the accompanying drawings in which:-

Figure 1 shows the dermal vasculature; by courtesy of Waverly Publishers- Williams & Williams Wilkins

Figure 2 is a graphic illustration of a signal derived from a probe embodying the present invention;

Figure 3a is a schematic drawing of a first embodiment of a probe

Figure 3b is an enlarged end view of the probe of Figure 3a;

Figure 4 is a schematic drawing of a second embodiment of a probe;

Figure 5 is a schematic drawing of a third embodiment of a probe;

Figure 6 is a schematic drawing of a fourth embodiment of a probe;

Figure 7 is a schematic drawing of a fifth embodiment of a probe;

Figure 8 is a schematic illustration of signal acquisition steps of a system embodying the present invention;

Figure 9 is a schematic illustration of the signal processing steps of a system embodying the present invention and

Figure 10 is a graph illustrating emitter and sensor voltages.

Figure 11 illustrates sample readings of Tissue Perfusion Index (TPI) compared with Tissue Oxygen saturation (TOS), at skin of forearm and finger, during staged occlusion of the brachial artery with a sphygmomanometer.

Detailed Description of Preferred Embodiments

Referring to the drawings Figures 3a and 3b shows a first design of a probe 10 embodying the present invention. The probe 10 comprises a high density, black polyethylene tube 12 which is 7mm in diameter and 105mm long which includes a light emitting and a light sensing element, 14 which as is best seen in Figure 3b is a circular, compounded light emitting and sensing device and is placed at the end of the tube. The element 14 comprises a central emitter 16 and an array of surrounding sensors 18. The emitter emits a pulsed light source. An electrostatically shielded cable 20 transfers the electrical signal from the probe 10 to signal processing electronics. Depending on the application, the number of sensors or more than one emitter may be used. For example, in Figure 3B, an alternate probe design may comprise a central sensor with one or more emitters.

The principal of operation of the system of the present invention is as follows.

The absorption of light entering a tissue can be said to follow the Beer-Lambert law of attenuation. Consequently, any backscattered light that reaches the sensors 18 is derived primarily from that region of tissue closest to the sensor.

The time varying signal is generated by absorptance levels of the incident infared light from the probe which falls on the observed tissue's microcirculation during the filling and partial emptying of the microcirculation with blood at each heart beat. The peak wavelength response of the emitter and sensor are approximately matched and include the isobestic point (805nm) on the absorption curves of oxygenated and deoxygentated blood. Importantly, the extravascular interstitial tissue enmeshing the microcirculation is relatively non-absorbent of light at this wavelength in comparison to the pulsatile blood flow of the capillary bed. This means that the backscattered light changes markedly in response to the pulsatile changes in the microcirculation.

As the microcirculation is filled during systole, light absorption increases and light back-scattered to the probe falls. The system circuitry records this fall in backscattered light as indicative of more red blood cells being present in the observed field and proportionally increases the probe's signal. Conversely, as the microcirculation empties during diastole, absorption decreases (and so backscattered light increases), and the probe signal level falls. Consequently, the degree to which the signal rises and falls is closely related to the pulsatile volume of red blood cells passing through the observed field at any instant. This resulting signal is integrated over each heart beat (corresponding to the area under the pulse curve), and multiplied by the heart rate. These products are then averaged over a pre-determined minimum short running time frame to provide an index of tissue perfusion, (that is, the TPI). Put mathematically:

$$\text{TPI varies as } \text{Curve Area (average)} \times \text{Heart Rate (average)}$$

Hence in a given running time frame,

$$\text{TPI varies as } \frac{\text{Red Cells}}{\text{Cardiac cycles}} \times \frac{\text{Cardiac Cycles}}{\text{Minute}}$$

$$\text{TPI varies as } \frac{\text{Red Cells}}{\text{Minute}}$$

That is, the TPI varies in proportion to any changes in observed capillary blood flow at any given time.

The TPI may be directly expressed as:

$$TPI = \int A \times HR \times k$$ where:

A = running value for area under signal curve
HR = value for Heart Rate
k = physiological constant for specific tissue

Figure 2 illustrates the form of a typical time varying signal derived from capillary bed by a probe. Figure 8 is a schematic diagram which sets out the key functional blocks in the signal acquisition by the system of the present invention.

A significant innovation in the present invention is the use of a pulsed light source. The pulsed light source enables data acquisition from a signal relatively free of background artifact ("noise") due to interference from ambient light. This enables tissue to be observed, either from a stand-off position across an air gap (for example, 30mm), or using fibre optic bundles to direct a highly focused light source to the target tissue, or provide highly focused sensors to collect light from specific locations. This ability to observe tissue at a distance greatly expands the monitoring capabilities of the new system compared with the existing system and a number of possible novel uses of the system are set out below.

Figure 9 outlines the key signal processing blocks. The electrical signal from the light sensor undergoes Analog to Digital Conversion and the resulting data stream is then smoothed. Following peak detection of the differentiated data stream by use of an active threshold technique, the times at which maximums and minimums occurred in the data stream are determined. These time points are then used as markers to calculate (i) the heart rate (from the time between two successive minimums) and (ii) the TPI (pulse curve area x HR), during this interval. The resulting data streams are separately buffered, for example, the heart rate buffer acquires six seconds of data, while the TPI buffer acquires three seconds. The TPI is then multiplied by the TPI gain value set either manually or automatically using the current signal level as a reference for subsequent data acquisition. Subsequent TPI values are then compared to this Reference TPI to reflect change in tissue perfusion from an initial state, or tissue perfusion relative to a different location.

In clinical application, the TPI measures change in microcirculation as it occurs from an initial reference level. For example, if the system is being used to monitor a patient during general anaesthesia, the base reference would be established with the patient in a settled state prior to anaesthesia.

As a second example, if the system is used to assess capillary activity in a target tissue, for example, a site of inflammatory or neoplastic tissue in skin, the reference level would be taken from the adjoining normal skin.

The shape of the signal curve varies with tissue compliance to flow, as physiological or pathological changes in tissue are encountered and so the time point estimates of TPI signal are also used to calculate other characteristics of the signal curve (for example, the rise time and fall time) which is one characteristic of signal shape. The changes in signal curve shape are expressed as variations in rise time T_r (msec) and fall time T_f (msec). These analysis techniques are described in the Prior Art (refer US Patents 3,796,214 and 4,442,845), the entire contents of which are incorporated herein by reference.

The system is controlled using a Personal Computer interface, not illustrated. Signal processing and display parameters are controlled using keystrokes and the waveform(s) and signal characteristics are displayed on the computer monitor in real time. These digitised signals may also be optionally logged as a digital file for recording and post-processing.

The PC interface provides a multitude of options of display of the information. For example, if the system is being used during anaesthesia, a declining TPI can indicate compensatory vasoconstriction of skin from blood loss and warning of impending cardiovascular shock. A declining TPI can also indicate clinically non-evident accumulating tissue oedema (for example, from excess intravenous saline) osmotically compromising the capillary bed. The clinician is alerted to these otherwise unknown important disturbances by an optional on/off alarm system which sounds if the TPI, calculated as a moving average figure, moves beyond a predefined range for a finite time (for example 8 seconds) from an initial reference level. The changes in tissue perfusion of the targeted organs are identified for the clinician long before macro-parameters such as blood pressure, heart rate or tissue oxygen saturation, all late indicators of disturbance, show any change.

Alternatively, the system's display can be configured to capture and display the TPI at various locations of the targeted tissue to monitor its viability

(for example, assessing the return of blood supply to a skin graft or characterising the microcirculation of a skin lesion, or at the border of a skin lesion).

Figure 4 illustrates a second embodiment of a probe 30 in which two high density polyethylene tubes 32, 34 are located side by side. One tube 32 contains a light emitting device 36 arranged to emit a pulsed light source and the other tube 34 contains a light sensing device 38. An analogous implementation using fibre optic cable could be readily employed to provide much smaller, more flexible probe designs using this approach.

Figure 5 illustrates yet a further probe design in which a light emitter 40 and a light sensor 42 are mounted side by side close to the end of a tubular probe 44, suitable for the observation of intrauterine and cervical tissue or for intra-rectal examinations.

Figure 6 illustrates yet a further probe 60 which may be transparent and is approximately 20mm long x 15mm wide x 3.5mm deep and can be used as a multi-purpose probe for analysing microcirculation at a point of observation on the skin surface. The back of the probe incorporates marks 62 over the sensor to facilitate alignment. The skin may be marked to enable alignment of the sensor over the targeted area of tissue 64.

Figure 7 illustrates yet a further probe 70 which is mounted on adjustable legs 72 to facilitate placement. The optical elements of the probe may be mounted in a telescopic tube to enable different areas of tissue to be examined, such as a skin lesion 74.

In basic application the previous system described in earlier prior art has been invaluable for detection of autonomic disturbances such as due to lightness of anaesthesia, or for correction at skin level of a trend to preshock and for accurate blood replacement following blood loss. However, the invention described herein incorporating a pulsed light source greatly expands the monitoring capabilities to enable assessments of important tissue viability in previously difficult to access areas. Such areas may include:

- observations of damaged tissue in burns units,
- variations in re-vascularisation of tissue in trauma units and in the field of dermatology or following skin grafting, or in the management of post-operative wound breakdown,
- assessment of retinal microcirculation by splitting and processing back reflected light from a light beam in a slit lamp optical instrument,

- assessment of viability of tooth pulp tissue through the enamel of the crown of the tooth,
- the use of two way fibre optic bundles allows viability in difficult to access organ tissues to be monitored, eg, through a ureter to the pelvis of a transplanted kidney,
- assessment of peripheral microcirculation provides characteristic waveforms that are triggered by various central nervous system status changes (for example, a stage of sleep) or autonomic status change (for example, such as autonomic afferent activity from a full bladder).
- In yet another application, arterial stenoses may be located by observing the changes in the TPI reading during sequential occlusion of each of the arterial supply vessels by direct pressure. In this particular application, the TPI is a diagnostically valuable supplement to other vascular diagnostic methods (e.g. Ultrasound Doppler systems) and
- In the field of neurology, the responses in microcirculation to sympathetic blockade and to reflex autonomic influences on tissue blood flow activity and signal curve analysis, can be accurately observed and recorded.

While this application describes one embodiment of the invention, other variations in signal acquisition design to achieve the same capabilities are possible. For example, data may be acquired while the light emitter is switched off, to provide an active sample of background noise, which can then be digitally subtracted from the signal. Alternatively, active notch filters may be applied (for example at 50/60 and 100/110Hz – the most common frequencies of incandescent light) to actively remove background noise before data analysis. As noted there are a wide range of probe designs of which several examples are disclosed.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this seventeenth day of October 2002

Perfusion Diagnostics Pty Ltd
Patent Attorneys for the Applicant:

F B RICE & CO

Figure 1

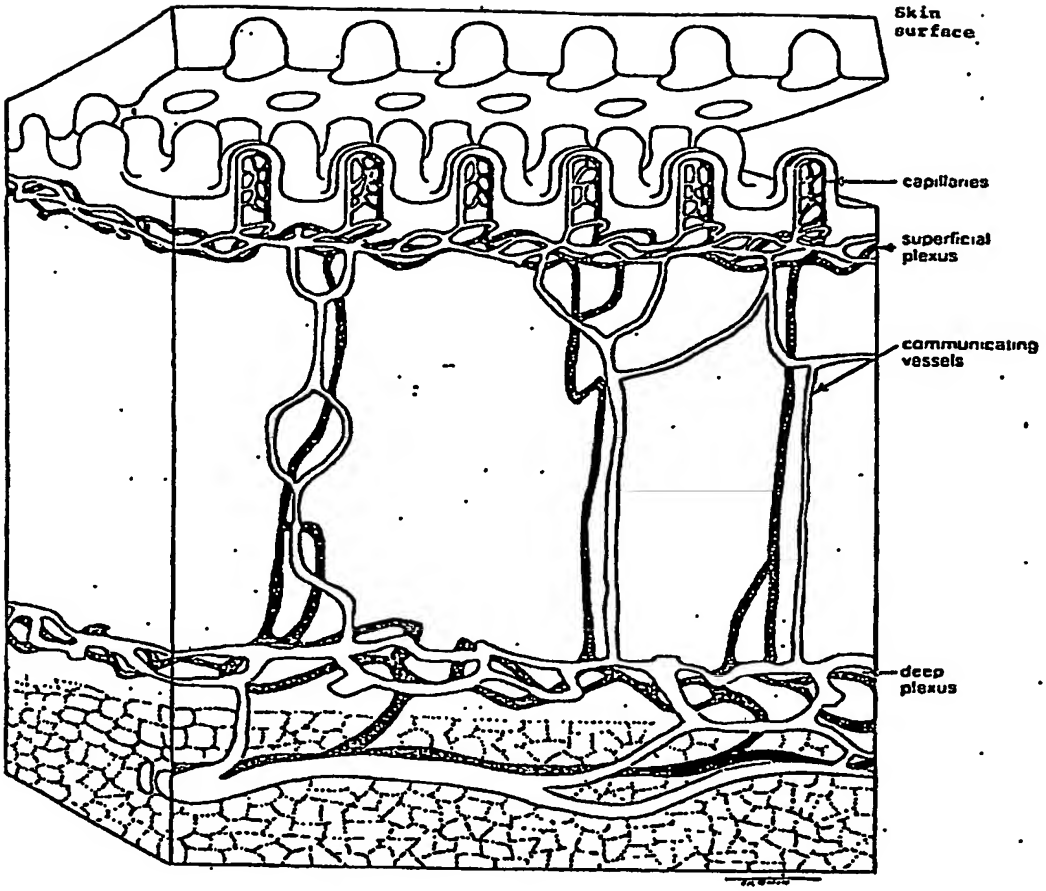


Figure 2

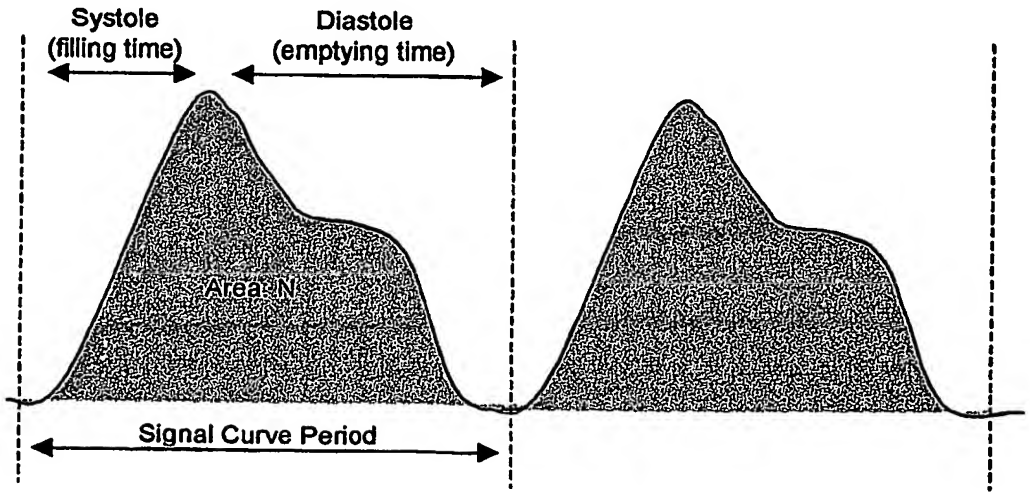


Figure 3A

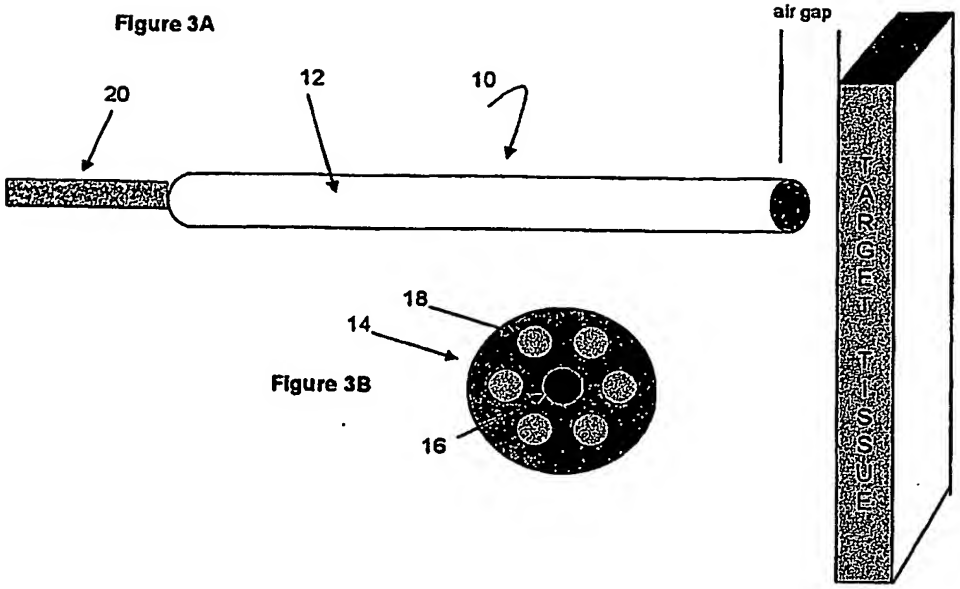


Figure 3B

Figure 4

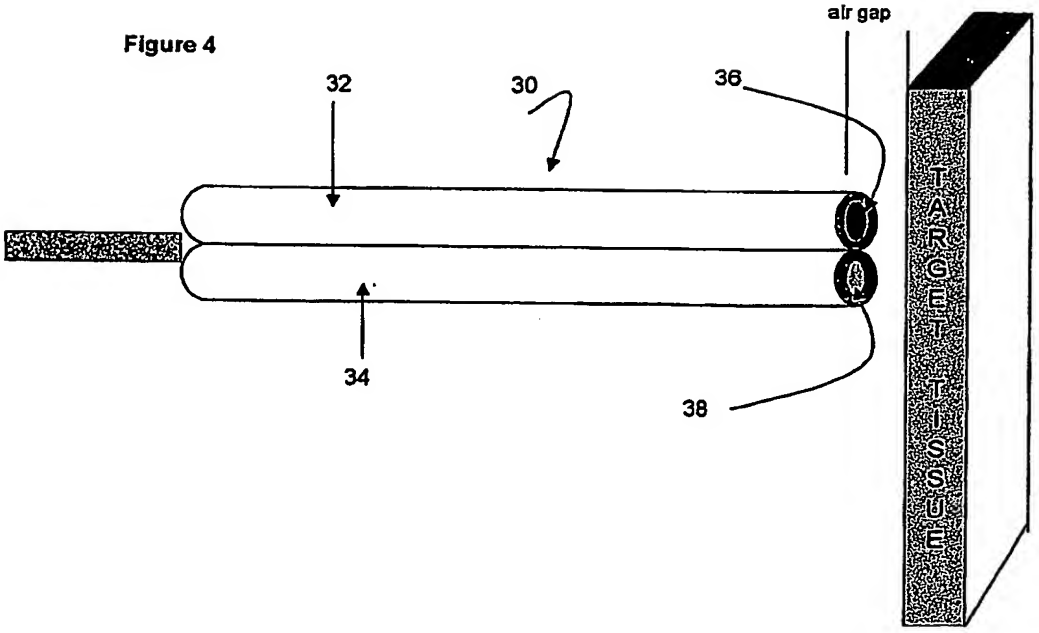


Figure 5

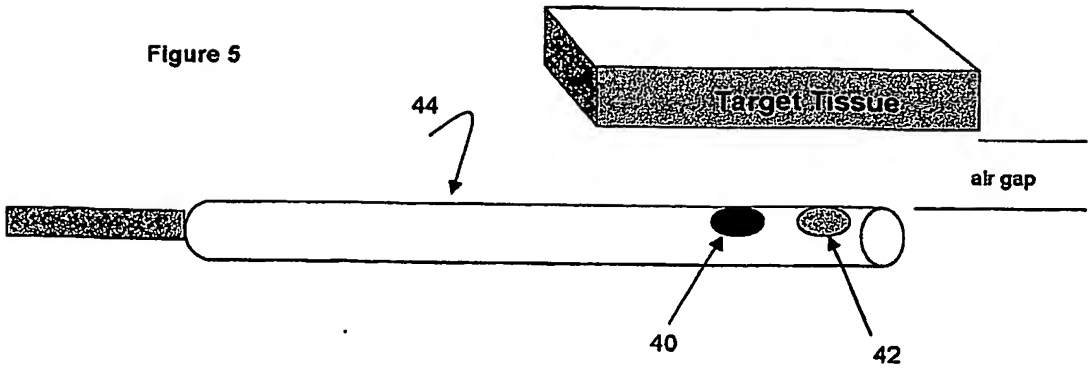


Figure 6

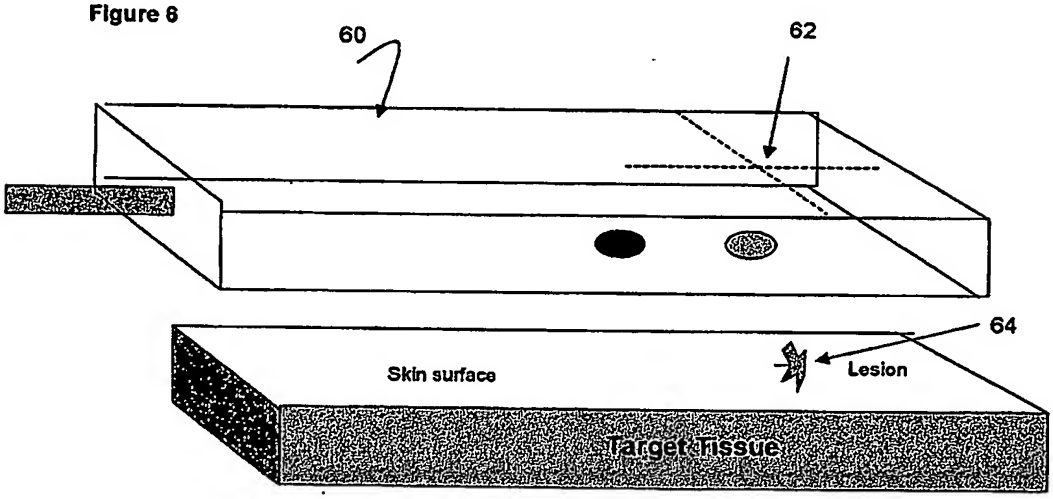


Figure 7

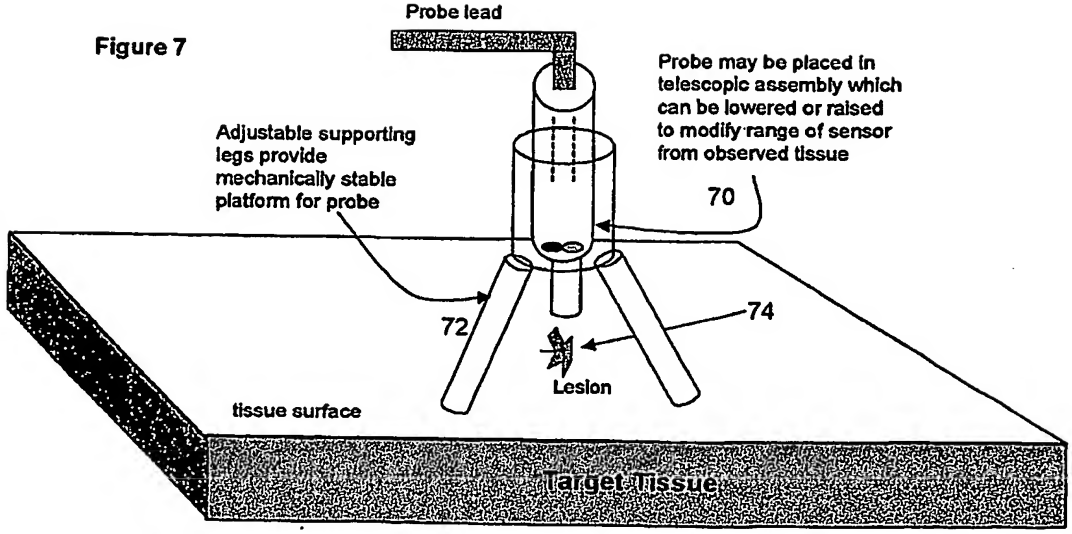


Figure 8

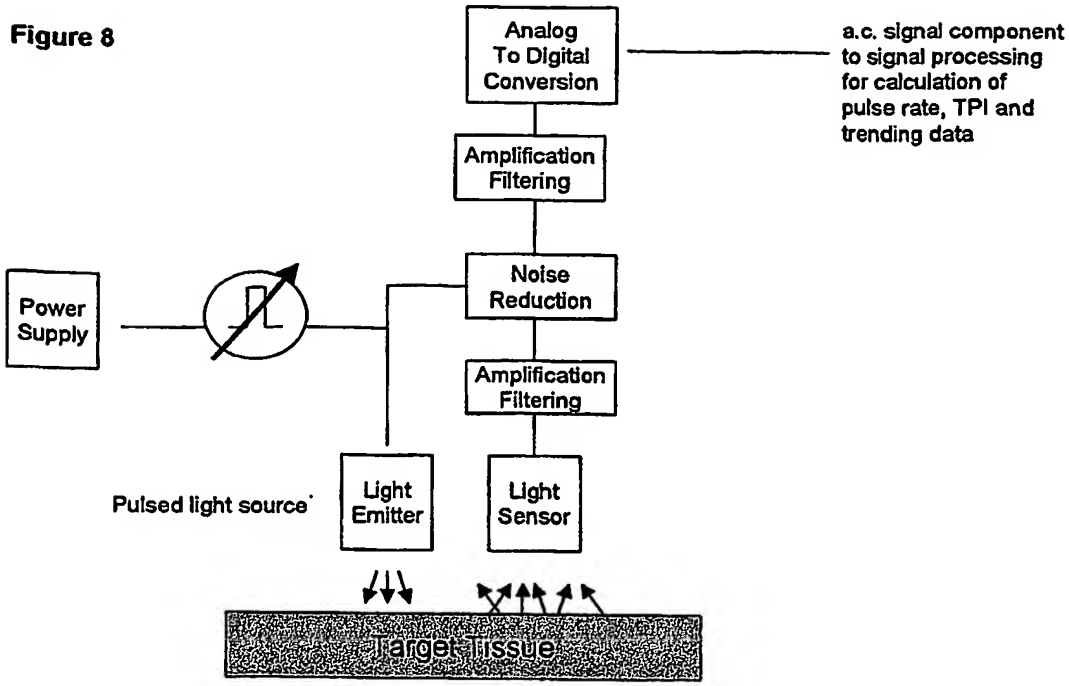


Figure 9

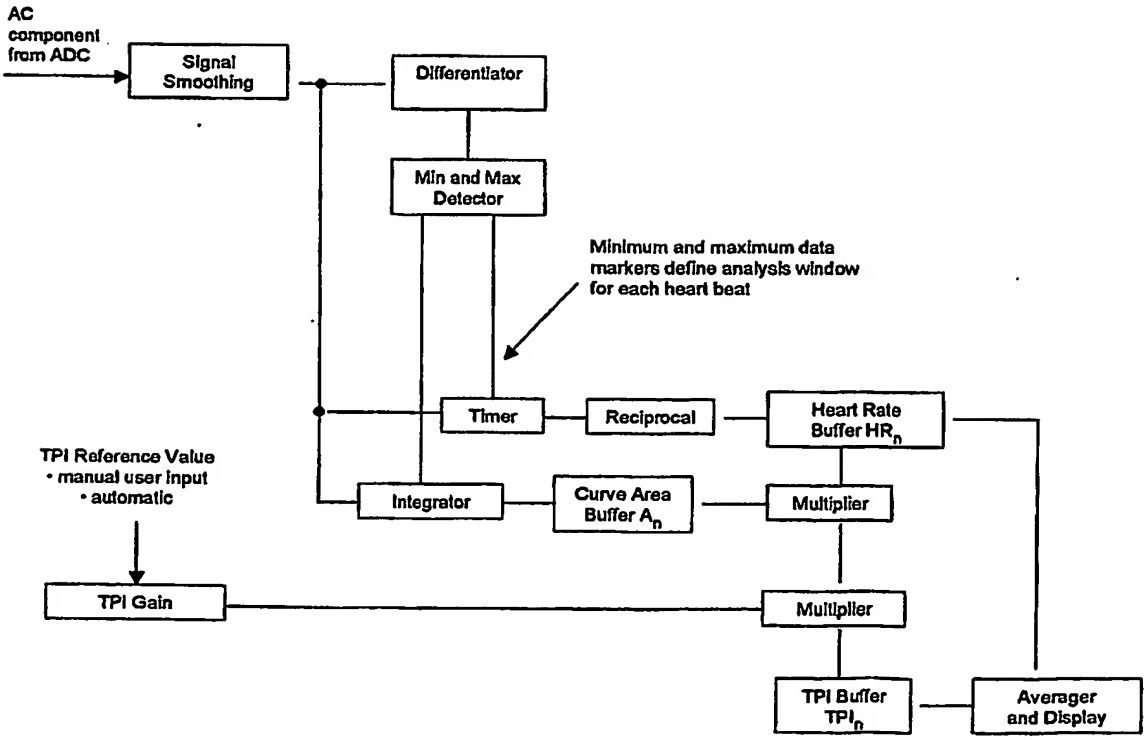
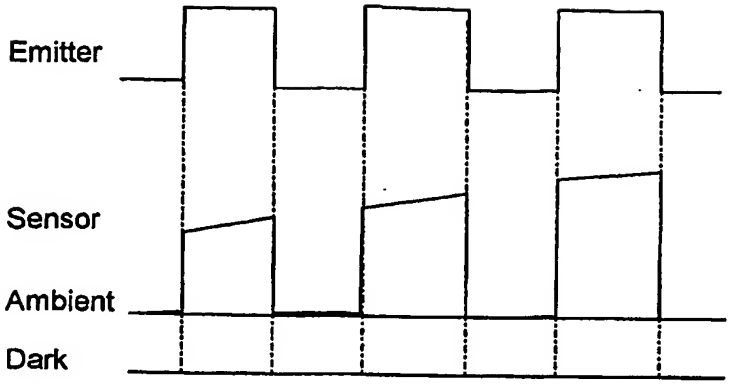


Figure 10



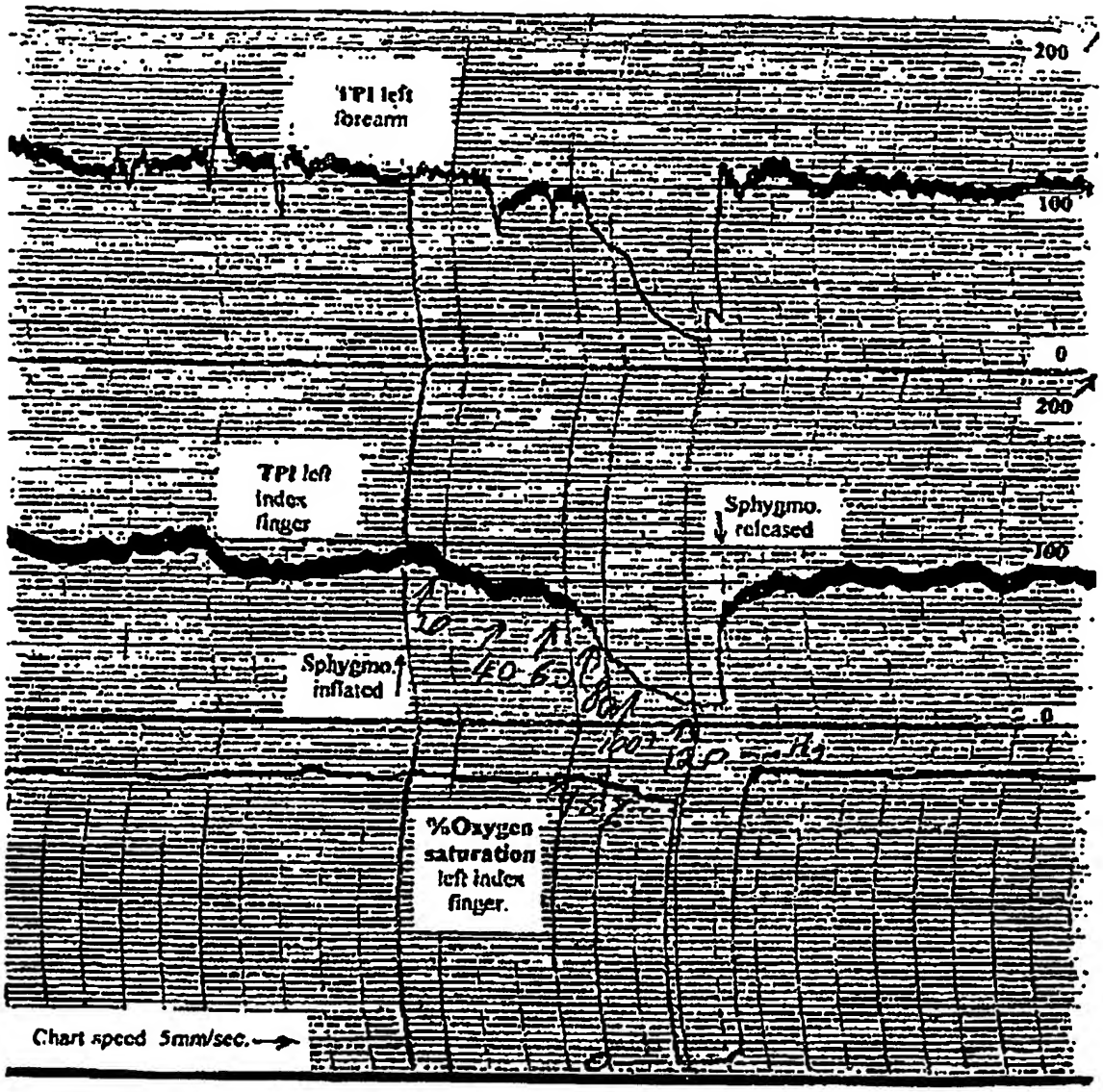


Figure 11. Readings for Tissue Perfusion Index (TPI) and Tissue Oxygen Saturation (TOS) at skin of the forearm and skin of the digit are compared during staged occlusion of the brachial artery with a sphygmomanometer. A fall of almost 90% in TPI occurs before significant change in TOS. A reproducible figure illustrating capillary reserve.